Comparison of silver sulfadiazine and gentamicin for topical prophylaxis against burn wound sepsis

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Daily prophylactic application of either 1.0% silver sulfadiazine cream or 0.1% gentamicin cream was compared for effectiveness in preventing bacterial colonization of burn wounds and sepsis. *Pseudomonas aeruginosa* **colonized the wounds of 37% of the 38 patients treated with silver sulfadiazine and 30% of the 33 patients treated with gentamicin; gentamicin-resistant** *P. aeruginosa* **colonized the wounds of 21% of the patients treated with gentamicin.** *Staphylococcus aureus* **colonization occurred in 55% of the patients treated with silver sulfadiazine, whereas colonization with** *Candida* **species occurred in 58% of the patients treated with gentamicin. Although gentamicin-resistant organisms caused no deaths their repeated appearance resulted in discontinuation of prophylaxis with gentamicin cream. The next year** *P. aeruginosa* **strains resistant to gentamicin were isolated from burn wounds of only two patients who had not previously received parenteral therapy with gentamicin or tobramycin. Gentamicin cream should be reserved for treating patients with wounds infected by gentamicin-sensitive** *P. aeruginosa* **and those allergic to sulfa drugs. For most patients with burn wounds silver sulfadiazine is safe and effective as an antibacterial agent for topical prophylaxis.**

Des applications quotidiennes d'une crème de sulfadiazine d'argent à 1.0% ou d'une crème de gentamicine à 0.1% ont été comparées pour leur efficacité respective dans la prévention de la colonisation bactérienne des brûlures et de la septicémie. Le *Pseudomonas aeruginosa* **a colonisé les brûlures de 37% des 38 patients traités à la sulfadiazine d'argent et de 30% des 33 patients traités à la gentamicine; des souches de** *P. aeruginosa* **résistantes à la gentamicine ont colonisé les brûlures de 21% des patients traités à la gentamicine. Une colonisation par le** *Staphylococcus aureus* **est survenue chez 55% des patients traités à la sulfadiazine d'argent, alors qu'une colonisation par** *Candida* **sp. a été observée chez 58% des patients traités à la gentamicine. Bien que les germes résistants à la gentamicine n'aient entraîné aucun décès, leur apparition répétée a résulté en l'arrêt du traitement préventif avec la crème à la gentamicine. L'année suivante, des souches de** *P. aeruginosa* **résistantes à la gentamicine ont été isolées des brûlures de seulement deux patients qui n'avaient pas reçu précédemment de gentamicine ou de tobramycine. La crème à la gentamicine devrait être réservée au traitement des patients ayant une plaie infectée par une souche de** *P. aeruginosa* **sensible à la gentamicine et de ceux qui sont allergiques aux sulfamidés. Pour la plupart des brûlés la sulfadiazine d'argent est sûre et efficace comme agent antibactérien en traitement prophylactique local.**

Gentamicin has been widely used in Canada for topical prophylaxis against burn wound sepsis. Since 1969 our burn units had routinely used gentamicin topically, with satisfactory results. However, the appearance of gentamicin-resistant *Pseudomonas aeruginosa* in the wounds of 25% of the 130 patients so treated caused concern.[1] After a long period of evaluation[2-4] silver sulfadiazine became commercially available in 1975. To compare the effectiveness of these two agents in preventing bacterial colonization and sepsis in burn wounds, we treated 71 patients having major burns with daily application of either silver sulfadiazine or gentamicin during an 18-month period.

Methods

Patient selection

To be eligible for the study a patient had to have been admitted within 24 hours of being burned, had to have a burn covering more than 10% of the body surface and could not have previously received topical antibacterial therapy. Adults and children were treated in separate burn units, each of which was part of a general plastic surgery ward at the Health Sciences Centre, Winnipeg. Within the adult and pediatric groups eligible patients were subdivided into two groups — those with smaller burns (covering 11% to 40% of the body surface) and those with larger burns (covering 41% or more of the body surface). Within each group the patients were numbered consecutively in order of admission. The odd-numbered patients were treated with silver sulfadiazine and the even-numbered with gentamicin. Patients treated for less than 7 days were removed from the study. Between July 1974 and January 1976, 49 adults and 22 children qualified for the patient group studied.

Wound care

All patients were bathed daily in tap water in a Hubbard tank (Hubbard Scientific Co., Northbrook, Illinois) with a disposable liner; compressed air bubbles introduced through perforations in the liner agitated the water. The wound was covered with a thin layer of either 1.0% silver sulfadiazine cream, in 38 patients, or 0.1% gentamicin cream (Garamycin), in 33 patients, and dressings were applied to all areas except the face and perineum. The silver sulfadiazine cream used for the first 6 months of the study was prepared in the hospital pharmacy; thereafter a commercial product (Flamazine) was used. Patients with burns of the eyelids were treated with sulfacetamide sodium ointment or eyedrops (Sodium Sulamyd) if they were receiving silver sulfadiazine therapy, or polymyxin B–neomycin ointment (Neosporin) or gentamicin ointment (Garamycin) if they were receiving gentamicin therapy. Five patients being treated with silver sulfadiazine and two patients being treated with gentamicin were also treated with the debriding agent sutilains (proteolytic enzymes derived from *Bacillus subtilis*), as an oint-

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ment (Travase), during the first 7 to 10 days after the burn. To exclude any influence the sutilains may have had on bacterial colonization we did not consider in subsequent data analysis organisms isolated from the wound during the period of application of this agent or for 7 days thereafter.

Daily application of the antibacterial agents was continued until the wound was healed in patients with partial-thickness burns, and until the first grafting procedure was completed in patients with full-thickness burns. In some patients daily application to all nongrafted full-thickness burns continued uninterrupted after grafting, while in others daily application was interrupted or stopped after the first grafting procedure.

Systemic antibiotic therapy

Penicillin or erythromycin was given during the first week to all except five patients to prevent colonization with group A streptococci. Thereafter antibiotics were used systemically as necessary to treat recognized established infection. Methicillin was chosen for infection with *Staphylococcus aureus* and carbenicillin for infection with *P. aeruginosa*.

Bacteriologic studies

Swabs were taken from one or two representative areas of the burn wound every Monday and Thursday and cultured aerobically. Growth was rated from 0 to 4+. Colonization was defined as 2+ growth or more of the same species from swabs obtained on two or more consecutive sampling days. The requirement for serial isolation eliminated the consideration of transient flora. Sensitivity to gentamicin was determined for all *P. aeruginosa* isolates by the disc method of Bauer and Kirby[5] and the agar dilution technique of Steers, Foltz and Graves.[6] The organism was considered to be resistant if the zone of inhibition around the 10-μg disc was 12 mm or less and the minimum inhibitory concentration was greater than 12.5 μg/mL. Pyocine typing by a modification of the method of Govan and Gillies[7] was done on all isolates of *P. aeruginosa* from burn wounds and on all isolates from other patients on the ward during the study period. The resulting information was used to determine if patient-to-patient transfer of resistant strains was occurring or if a reservoir of resistant organisms existed on the burn ward. Episodes of burn wound sepsis and septicemia were noted and the responsible organisms were identified in each group.

Follow-up study

The comparative study ended in January 1976, and the last patient treated topically with gentamicin was discharged 2 months later. Between April 1976 and April 1977 wound colonization was monitored by the same method as during the study period and identical studies of *P. aeruginosa* isolates were carried out.

Results

Patient characteristics

The characteristics of each group of patients are detailed in Table I. The groups were comparable with respect to age and extent of burn except that a higher proportion of patients receiving silver sulfadiazine therapy than of patients receiving gentamicin therapy (80% v. 63%) had third-degree burns.

Table I—Characteristics of groups of patients with burns treated prophylactically with applications of silver sulfadiazine or gentamicin

Characteristic	Silver sulfadiazine	Gentamicin
No. of patients		
Total	38	33
Aged 15 years or less	12	10
Mean age, yr	31	33
Mean surface area burned, %	30	29
No. of patients with third-degree burns	30	21
Mean surface area with third-degree burns, %	17	18
No. of deaths		
Expected	9.0	9.6
Actual	4	3
Mean no. of consecutive days of topical therapy	25	25
Mean interval from burn to first grafting, days	26	23

Colonization of burn wounds

The proportions of patients in each group whose wounds were colonized with various organisms are compared in Table II. *P. aeruginosa* colonized the wounds of 37% of the 38 patients treated with silver sulfadiazine and 30% of the 33 patients treated with gentamicin. The other gram-negative organisms, except for the nonfermenting organism *Alcaligenes faecalis*, were more common in the group treated with silver sulfadiazine. *S. aureus* colonization of wounds occurred in 55% of the patients treated with silver sulfadiazine but only 21% of those treated with gentamicin, while *Candida* colonization occurred in 58% of the patients treated with gentamicin but only 11% of those treated with silver sulfadiazine. Although freedom from bacterial colonization of wounds during the entire treatment period was more frequent in the gentamicin-treated group, fungal colonization was much more frequent in this group than in the group treated with silver sulfadiazine (58% v. 11%).

Table II—Proportions of patients whose wounds were colonized during entire course of treatment

Organism	% Silver sulfadiazine	% Gentamicin
Gram-negative bacteria		
Pseudomonas aeruginosa	37	30
Escherichia coli	26	6
Alcaligenes faecalis	3	12
Enterobacter	13	0
Klebsiella	11	0
Proteus	5	0
Acinetobacter	3	0
None isolated	53	66
Gram-positive bacteria		
Staphylococcus aureus	55	21
Streptococcus faecalis	11	6
Staph. epidermidis	11	3
Group A streptococci	5	6
Staph. viridans	8	0
None isolated	34	75
Fungi		
Candida	11	58
None isolated	89	42

P. aeruginosa colonization

Data for *P. aeruginosa* colonization in the two treatment groups are compared in Table III. In seven patients treated with gentamicin the

Table III—*P. aeruginosa* colonization of wounds

Datum	Silver sulfadiazine	Gentamicin
No. of patients		
Total	38	33
With colonization by all strains	14	10
With colonization by gentamicin-resistant strains	2	7
While receiving daily application of antibacterial	2	6
Average interval from burn to initial isolation, days	28	21

wounds were colonized by a gentamicin-resistant strain of *P. aeruginosa;* in six of the seven the resistant strains appeared during the period of consecutive daily application of gentamicin. Resistant strains appeared on average 19 days after topical antibacterial therapy was begun.

Pyocine typing was used to identify strains of *P. aeruginosa* colonizing the wounds of more than one patient at the same time; the results are shown in Table IV.

Table IV—Results of pyocine typing of strains of *P. aeruginosa* colonizing the wounds of more than one patient

Unit and type	No. of patients
Children's	
1j	4
Adult	
1j	3
1g	2
5	2
10	2

In four of the six children whose wounds were colonized with *P. aeruginosa* the strain was type 1j. Three of the four children were treated within a 3-month period; a resistant strain was isolated from the wounds of the first patient treated, but only sensitive strains were isolated from the wounds of the two patients treated subsequently. The fourth child's wounds were colonized with a sensitive 1j strain 6 months later. A further 9 months later a brother and sister of almost identical weight and distribution of burns (covering 50% of the body surface) were treated, one with each agent, in the same room. They were bathed in random order in the same tub. The wounds of the child receiving gentamicin were colonized with a type 34 strain, which became resistant 35 days after the child was burned. Two weeks after that strain became resistant the wounds of the other child became colonized with a sensitive organism of a different but untypable strain.

Among the 18 adults whose wounds were colonized with *P. aeruginosa* a few pyocine-type strains were identified in more than one patient, but not at the same time. Never did a particular resistant strain colonize the wounds of more than one patient at the same time. These findings indicated that patient-to-patient transmission of resistant strains was not occurring and that no reservoir of resistant organisms existed on the burn ward.

Gentamicin-resistant *P. aeruginosa* colonized the wounds of two patients treated with silver sulfadiazine. One had completed 10 days earlier a 5-day course of gentamicin administered intravenously because of burn wound sepsis caused by *Enterobacter*. The other had been treated with polymyxin B–neomycin ointment for eyelid burns, although the protocol called for sulfacetamide sodium ointment.

Burn wound sepsis and septicemia requiring treatment

Data for the patients with burn wound colonization who required systemic antibiotic treatment are compared in Table V. In some patients more than one organism was isolated. Two patients treated with silver sulfadiazine died of septicemia, one of *Klebsiella* infection 35 days after being burned, and the other of *S. aureus* infection of a decubitus ulcer after skin grafting was complete. Five of the nine patients whose wounds were colonized by resistant *P. aeruginosa* had burn wound sepsis and one of them also had septicemia; all were successfully treated with carbenicillin.

Table V—Data for cases of burn wound sepsis and septicemia

Datum	No. of patients with sepsis (and with septicemia)	
	Silver sulfadiazine (n=11[4])	Gentamicin (n=7[2])
Organism		
P. aeruginosa	7	3 (1)
S. aureus	5 (2)	3
Klebsiella	3 (2)	0
Enterobacter	2	0
Fungi	0	2 (1)
Death		
Due to burn wound sepsis	2*	0
Due to pulmonary complications	2	3

*With *Klebsiella* in one instance and *S. aureus* in the other.

Mortality

The patients in this study were preselected in that all had survived for 7 days after being burned. The expected mortality, calculated from the mortality probability chart of Bull,[8] and the actual mortality in each group are shown in Table I. In the silver sulfadiazine group two patients died from burn wound sepsis; two other patients died of pneumonia. In the gentamicin group two patients died of pulmonary edema and one of pneumonia.

Results of follow-up study

Between April 1976 and April 1977, 82 patients with fresh burns of all sizes were treated, 25 with silver sulfadiazine cream, 19 with framycetin sulfate (Sofra-Tulle) as a tulle gras dressing, 5 with povidone–iodine and 33 with no topical antibacterial. The prophylactic use of gentamicin had been discontinued in January 1976. The wounds of 18 patients were colonized by *P. aeruginosa* (Table VI). The strains were gentamicin-resistant in eight patients, seven of whom had been treated with silver sulfadiazine and one of whom had not been treated with applications of an antibacterial (Table VII). Of these eight patients five had received gentamicin and one tobramycin parenterally before the resistant strain appeared; the other two had not previously received parenteral aminoglycoside therapy. Of the 10

Table VI—Aminoglycoside therapy preceding *P. aeruginosa* colonization of wounds after discontinuation of the prophylactic topical use of gentamicin

Aminoglycoside given parenterally before isolation	Strain; no. of patients	
	Gentamicin-sensitive (n = 10)	Gentamicin-resistant (n = 8)
Gentamicin	0	5
Tobramycin	0	1
None	10	2

Table VII—Data for cases of *P. aeruginosa* colonization after discontinuation of the prophylactic topical use of gentamicin

Datum	Strain	
	Gentamicin-sensitive	Gentamicin-resistant
No. of patients		
Total	10	8
Receiving topical therapy		
Silver sulfadiazine	5	7
Povidone–iodine	2	0
Framycetin sulfate	1	0
None	2	1
Surface area burned, %		
Mean	11	40
Range	3–21	9–86
Interval from burn to initial isolation, days		
Mean	19	26
Range	4–53	9–70

patients with gentamicin-sensitive strains 2 subsequently received gentamicin topically and systemically and the organisms were eliminated without subsequent appearance of resistant strains. In general the burns were much more extensive in the patients from whom resistant organisms were isolated, and the resistant strains appeared on average 1 week later than the sensitive strains (Table VII).

Discussion

Neither silver sulfadiazine nor gentamicin used topically prevented microbial colonization of burn wounds. *P. aeruginosa* colonized the wounds of 37% of the patients treated with silver sulfadiazine and 30% of the patients treated with gentamicin.

The main problem revealed in this study was the continued appearance of gentamicin-resistant *P. aeruginosa* in the wounds of patients treated topically with gentamicin, an antibacterial agent that has been recommended specifically to suppress this organism. Moreover, the resistant strains disappeared 3 to 4 weeks after cessation of the topical use of gentamicin in half of these patients. Pyocine typing ruled out patient-to-patient transfer as a cause of perpetuation of these strains.

The appearance of gentamicin-resistant *P. aeruginosa* after cessation of the routine prophylactic topical use of gentamicin was infrequent when neither gentamicin nor tobramycin had previously been used parenterally, occurring in 2 (2%) of 82 patients. This seems comparable to the frequency of de novo appearance of resistant strains noted previously in this hospital.[9] Resistant strains tended to colonize larger burns. Therefore, 7 years' use of gentamicin applied to burn wounds did not appear to produce a reservoir of a particular resistant strain in our burn units.

MacMillan and associates[10] could not identify environmental sources of resistant strains but found that these strains were confined to patients undergoing topical and systemic treatment with gentamicin. Gamon and colleagues[9] cultured *P. aeruginosa* from specimens from 238 patients; of the 12 patients found to harbour resistant strains 10 had been treated topically or systemically with gentamicin. No evidence of in-hospital spread of resistant strains could be found. Stone and Kolb[11] demonstrated a reservoir of gentamicin-resistant strains in the hydrotherapy tank, particularly the aerators and agitators, used for patients with burns. The tank and the hands of the nursing and physiotherapy personnel were the source of patient-to-patient transmission of resistant organisms; however, after the prophylactic topical use of gentamicin in patients with burns was stopped the resistant strains disappeared from the tank.

Both MacMillan and associates[10] and Stone and Kolb[11] reported that generalized sepsis did not develop in patients from whom resistant strains were isolated. Stone and Kolb[11] noted that no patient with resistant pyocine-type 5 flora exhibited urinary excretion of verdohemoglobin. MacMillan and colleagues[10] noted that the frequency of *Pseudomonas* sepsis decreased from 84% to 0% during the period of prophylactic gentamicin use, and that no cases of *Pseudomonas* sepsis were fatal. In our initial study,[1] in which the wounds of 25% of the patients treated prophylactically with gentamicin cream were found to be colonized with resistant strains of *P. aeruginosa,* no death was due to this organism. This was true in the 1975-76 study as well. The reasons for this might be reduced virulence of the resistant strains or prompt recognition of resistant strains and initiation of vigorous treatment to suppress their effects. Large doses of carbenicillin (400 mg/kg daily) have been effective in controlling invasion by gentamicin-resistant *P. aeruginosa.* However, the demonstrated ability of *P. aeruginosa* to become resistant to gentamicin precludes its routine topical use as a prophylactic agent in patients with burns.

The presence of *P. aeruginosa* resistant to gentamicin in two patients treated with silver sulfadiazine may have been related to the intravenous administration of gentamicin in one and cross-resistance between neomycin and gentamicin in the other.

Gentamicin should not routinely be used topically as a prophylactic antibacterial in patients with burns but should be reserved for patients whose wounds have become colonized with *P. aeruginosa.* In our patients 3 weeks elapsed on average after the initiation of gentamicin therapy before resistant strains appeared. This period can be crucial in a seriously burned patient. In addition, gentamicin used topically is an effective alternative prophylactic agent for a patient allergic to sulfa drugs.

Silver sulfadiazine is currently accepted as an effective, safe antibacterial agent. However, careful serial bacteriologic monitoring of the burn wound is necessary since, as we have demonstrated, a substantial percentage of patients' wounds were colonized by *S. aureus* and gram-negative organisms, particularly *P. aeruginosa.*

A search for the optimal antibacterial must continue. However, measures designed to augment the host's immunologic response, removal of the eschar as quickly and as atraumatically as possible, and coverage of the wound with autografts are equally important.

References

1. SNELLING CFT, RONALD AR, WATERS WR, et al: Topical gentamicin cream as prophylaxis against burn-wound sepsis. *Burns* 2: 128, 1976
2. FOX CL JR, RAPPOLE BW, STANFORD W: Control of pseudomonas infection in burns by silver sulfadiazine. *Surg Gynecol Obstet* 128: 1021, 1969
3. HUMMEL RP, MACMILLAN BG, ALTEMEIER WA: Topical and systemic antibacterial agents in the treatment of burns. *Ann Surg* 172: 370, 1970
4. LOWBURY EJL, JACKSON DM, RICKETTS CR, et al: Topical chemoprophylaxis for burns: trials of creams containing silver sulfadiazine and trimethoprim. *Injury* 3: 18, 1971
5. BAUER AW, KIRBY WMM, SHERRIS JC, et al: Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 45: 493, 1966
6. STEERS E, FOLTZ EL, GRAVES BS: An inocula replicating apparatus for routine testing of bacterial susceptibility to antibiotics. *Antibiot Chemother* 9: 307, 1959
7. GOVAN JRW, GILLIES RR: Further studies in the pyocine typing of *Pseudomonas pyocyanea. J Med Microbiol* 2: 17, 1969
8. BULL JP: Revised analysis of mortality due to burns. *Lancet* 2: 1133, 1971
9. GAMON W, CATES C, SNELLING CFT, et al: Emergence of gentamicin- and carbenicillin-resistant *Pseudomonas aeruginosa* in a hospital environment. *Antimicrob Agents Chemother* 9: 474, 1976
10. MACMILLAN BG, EDMONDS P, HUMMEL RP, et al: Epidemiology of *Pseudomonas* in a burn intensive care unit. *J Trauma* 13: 627, 1973
11. STONE HH, KOLB LD: The evolution and spread of gentamicin-resistant pseudomonads. *J Trauma* 11: 586, 1971